REMARKS/ARGUMENTS

Claims 1-10, 12, 13 and 36-46 have been examined in the above identified application. Claims 11, 14-35, and 47-54 are withdrawn. Claims 38 and 45 have been canceled. Claims 1 and 36 have been amended. Support for the amendments can be found in the specification. Therefore, no new matter has been added. Reconsideration of the claims in light of the following remarks is respectfully requested.

Election of Species:

Applicant acknowledges the restriction of prosecution of the pending claims to the species of (1) angiotensin converting enzyme (ACE); (2) diabetes; (3) small molecule; (4) no election possible; and (5) serum. Applicant further acknowledges the Examiner's agreement that claims 1-10, 12, 13 and 36-46 are readable on the elected species of invention as well as the Examiner's withdrawal of the previous requirement for the fourth species election. Applicant acknowledges the Examiner's note that this requirement will be reinstated if any claims encompassing the species of "protein" are subsequently rejoined.

Claim Objections:

The Examiner has objected to claim 1 because it does not end with a period. Applicant has amended the claim to include a period. In view of the amendment, Applicant requests the objection be withdrawn.

Rejections Under 35 U.S.C. § 112:

Claims 1-10, 12, 13, 36, 37 and 39-46 stand rejected under 35 U.S.C. § 112, first paragraph. The Examiner believes that the specification is enabling for a method for identifying an agent that alters processing of a membrane protein of interest, comprising contacting the agent with an isolated animal host cell that expresses the membrane protein and at least one processing enzyme of the membrane protein, or a non-isolated host cell in a transgenic mouse expressing

hAPP and an processing enzyme thereof, or a non-isolated host cell that naturally expresses the membrane protein and at least one processing enzyme of the membrane protein, and detecting altered processing of the membrane protein to identify the agent that alters the processing of the membrane protein. In addition, the Examiner alleges that the specification does not reasonably provide enablement for a method for identifying an agent that alters processing of a membrane protein of interest, comprising contacting the agent with an animal host cell that expresses the membrane protein and at least one processing enzyme of the membrane protein, and detecting altered processing of the membrane protein to identify the agent that alters the processing of the membrane protein. The Examiner alleges that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Examiner asserts that the nature of the invention is a method of screening comprising contacting an agent with cells expressing a membrane protein and at least one processing enzyme of the membrane protein, and detecting altered processing of the membrane protein. The Examiner believes that the methods encompass use of a genus of host cells, including those that naturally express, or recombinantly, express the membrane protein and/or enzyme. Furthermore, the Examiner asserts that the genus of host cells includes both isolated host cells, as well as those that are found within an organism. In addition, the Examiner believes the genus of host cells encompasses cells from any animal species, including humans.

According to the Examiner, the specification asserts that the claimed screening methods can be performed in transgenic animals and provides examples of transgenic mice that express human amyloid precursor protein (hAPP) that were known in the art and can be used in the claimed method of screening. However, the Examiner alleges that there are no methods or working examples disclosed in the instant application whereby any multicellular animal other than mice expressing hAPP is demonstrated to express the encoded peptide. The Examiner asserts that the unpredictability of the art is very high with regards to making transgenic animals. The Examiner submits that the literature teaches that the production of transgenic animals by microinjection of embryos suffers from a number of limitations, such as the extremely low

frequency of integration events and the random integration of the transgene into the genome that may disrupt or interfere with critical endogenous gene expression citing as an example Wigley *et al. Reprod. Fert. Dev.* 6: 585-588, 1994 among other references. Thus, according to the Examiner, based on the art recognized unpredictability of isolating and using embryonic stem cells or other embryonal cells from animals other than mice to produce transgenic animals, and in view of the lack of guidance provided by the specification for identifying and isolating embryonal cells that can contribute to the germ line of any non-human mammal other than the mouse, such as dogs or cows, the skilled artisan would not have had a reasonable expectation of success in generating any and all non-human transgenic animals using ES cell technology.

Further, the Examiner submits that due to the large quantity of experimentation necessary to generate a transgenic animal expressing a membrane protein and/or secretase, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art that establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

While Applicant disagrees with the Examiner's rejections and do not acquiesce to the reasoning provided by the Examiner, claim 1 has been amended to further expedite prosecution of the present case. As amended, claim 1 reads "a method for identifying an agent that alters processing of a membrane protein of interest, comprising: contacting the agents with an animal host cell that expresses the membrane protein and at least one processing enzyme of the membrane protein, wherein the animal host cell is an isolated host cell, a non-isolated host cell in a transgenic mouse expressing the membrane protein and at least one processing enzyme of the membrane protein, or a non-isolated host cell that naturally expresses the membrane protein and at least one processing enzyme of the membrane protein; detecting altered processing of the membrane protein to identify the agents that alter the processing of the membrane protein;

and, identifying agents that are allosteric effectors of the membrane protein." Support for the amendments can be found, for example, at page 17, line 20 through page 18, line 23, and page 51, line 6 through page 54, line 3. Applicant notes that claims 38 and 45 have been canceled to incorporate the originally claimed subject matter into presently amended claim 1. Furthermore, claim 36 has been amended to read in-part "wherein the isolated animal host cell is a mammalian host cell." In view of the specification and the Examiner's comments, Applicant respectfully submits that the presently amended claims are sufficiently enabled. Applicant reserves the right to prosecute any subject matter encompassed by a cancelled claim in a related, co-pending application. Accordingly, Applicant requests that the Examiner reconsider and withdraw the rejections under 35 U.S.C. § 112 to claims 1-10, 12, 13, 36, 37 and 39-44 and 46.

Rejections Under 35 U.S.C. § 102:

Claims 1-7, 12, 13 and 36-46 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Hooper *et al.*, *Biochem J.* 321:265-279, 1997. According to the Examiner, the recitation of "for identifying an agent that alters processing of a membrane protein of interest" in the preamble of the claims from the instant application is interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed method over one from the prior art. As such, the Examiner believes that claim 1 encompasses any method comprising contacting an "agent" with an animal host cell that expresses both a membrane protein and a processing enzyme of the membrane protein, and detecting altered processing of the membrane protein. The Examiner asserts that Hooper *et al.* teaches in a section titled "Secretase Assays" that "[t]he majority of studies on membrane protein secretases have employed whole-cell systems utilizing either natural or recombinant cell lines that express both the membrane protein and its secretase." The Examiner submits that Hooper *et al.* further teaches, "...release of TGF-α, L-selectin, IL6R and APP from the surface of CHO cells can be blocked by both metallo-protease inhibitors (TAPI-2 and 1,10-phenanthroline) and serine-protease inhibitors..." The Examiner asserts that CHO cells are animal cells. Thus, the Examiner alleges that Hooper teaches a method that comprises contacting an agent (*e.g.*, a metallo- or serine protease inhibitor) with CHO animal cells that express a membrane protein (*e.g.*, APP) and its secretase and detecting altered (*e.g.*,

blocked) processing when the cell is contacted with an agent (metallo-protease or serine-protease inhibitors). The Examiner asserts that Hooper *et al.* further teaches that the elected species of membrane protein under consideration, ACE, cleavage is inhibited by TAPI-2, BB94 (batimastat) and BB2116. According to the Examiner, these teachings of Hooper *et al.* anticipate claim 1.

Regarding claim 1, the Applicant respectfully disagrees with the rejection and do not acquiesce to the Examiner's reasoning used to support such a rejection. However, to further expedite prosecution of the present case, claim 1 has been amended to read "a method for identifying an agent that alters processing of a membrane protein of interest, comprising: contacting the agent with an animal host cell that expresses the membrane protein and at least one processing enzyme of the membrane protein, wherein the animal host cell is an isolated host cell, a non-isolated host cell in a transgenic mouse expressing the membrane protein and at least one processing enzyme of the membrane protein, or a non-isolated host cell that naturally expresses the membrane protein and at least one processing enzyme of the membrane protein; detecting altered processing of the membrane protein to identify the agent that alters the processing of the membrane protein; and, identifying agent that is an allosteric effector of the membrane protein." As indicated in the section "Identification of Allosteric Effectors" at page 36 of the original specification, there is no required order for carrying out the presently claimed method steps. For example, identification of an allosteric effector can be performed as a secondary screen on agents that have been identified as effectors of membrane protein processing. Alternatively, libraries can be prescreened to identify allosteric effectors, prior to carrying out the other claimed steps of contacting the agents to the cells and detecting altered processing of the membrane protein.

As amended, Applicant respectfully submits that Hooper *et al.* does not teach each and every element of the present claims. For example, the reference does not teach or suggest "allosteric effectors" or "identifying agents that are allosteric effectors of the membrane protein." Hooper *et al.* teaches inhibitors of processing enzymes, such as metallosecretases. The inhibitors bind to the processing enzymes and do not act as allosteric effectors of the membrane

protein. However, in rejecting original claim 45, the Examiner attempts to broaden the teachings of the reference by alleging that protease inhibitors disclosed in the Hooper *et al.* are allosteric inhibitors. Allegedly, the specification does not provide a limiting definition of "allosteric effector." Therefore, the Examiner reasons that "allosteric inhibitor" encompasses any agent that changes the structure of the protein. Apparently, the Examiner believes that protease inhibitors are allosteric effectors because inhibition of the cleavage of the membrane protein produced by these inhibitors results in a different structure, *i.e.*, an intact membrane protein. Contrary to the Examiner's assertions, however, the specification at page 13, lines 26 through 32, does provide guidance for interpreting the term "allosteric effector." For example, the term "allosteric effector" refers to an effector agent that activates or inhibits a particular protein activity or interaction by specifically binding to the protein to change its conformation. "Allosteric effector of the membrane protein," thus, refers to an agent that *specifically binds to the membrane protein* and changes its conformation such that processing by one or more processing enzymes of the membrane protein is altered. The inhibitors in Hooper *et al.*, are not allosteric effectors, as they do not bind the membrane protein to change its conformation. And, in addition to failing to teach allosteric effectors, the reference provides no teaching on how to specifically identify an allosteric effector. Therefore, the reference cannot anticipate the pending claim. Accordingly, Applicant in view of the above amendments and remarks the Examiner is respectfully requested to reconsider and withdraw the rejection to claim 1 under § 102(b) as anticipated by Hooper *et al.*

According to the Examiner, claims 2 and 3 each encompass a method of claim 1 wherein the detecting of the altered processing comprises assessing the relative presence of a membrane protein fragment released from the surface of the cell. The Examiner alleges that in the teachings of Hooper *et al.* described above, the blockage of release of the ectodomain of the membrane protein indicates that the relative presence of the membrane protein fragment has been detected. Therefore, the Examiner believes that the teachings of Hooper *et al.* described above also anticipate claims 2 and 3.

As set forth above with regard to claim 1, Applicant disagrees with the rejection and respectfully submit that claims 2 and 3 are, at least, patentable for being dependent from claim 1. Claim 1 as currently amended is not anticipated by Hooper *et al.* Accordingly, dependent claims 2 and 3 are similarly not anticipated by the reference. Applicant requests the Examiner reconsider and withdraw the rejection to claims 2 and 3 under 35 U.S.C. § 102(b) as being anticipated by Hooper *et al.*

The Examiner asserts that claim 4 depends from claim 1 and encompasses "a membrane protein processing enzyme" that is "a protease." The Examiner believes that the teachings of Hooper *et al.* as described are inherently directed to an enzyme that is a protease because the release is blocked by protease inhibitors. Therefore, the Examiner alleges that the teachings of Hooper *et al.* also anticipate claim 4.

As set forth above with regard to claim 1, Applicant disagrees with the rejection and respectfully submit that claim 4 is, at least, patentable for being dependent from claim 1. Being a dependent claim, the claim incorporates all of the elements of its respective independent claim. Accordingly, Applicant requests the Examiner reconsider and withdraw the rejection to claim 4 under 35 U.S.C. § 102(b) as being anticipated by Hooper *et al.*

Claim 5 depends from claim 1 and has been described by the Examiner as reciting "wherein the altered membrane protein processing results in a decreased production of a fragment of the membrane protein released from the cell surface." According to the Examiner, in the teachings of Hooper *et al.* as described above, the blockage of release of the ectodomain of the membrane proteins inherently results in decreased production of the released fragment. Therefore, the Examiner alleges that the teachings of Hooper *et al.* described above also anticipate claim 5.

As set forth above with regard to claim 1, Applicant disagrees with the rejection and respectfully submit that claim 5 is, at least, patentable for being dependent from claim 1. Being a dependent claim, the claim incorporates all of the elements of its respective independent

claim. Claim 1 as set forth above is believe to be patentable over any disclose of Hooper *et al.* and accordingly, Applicant requests the Examiner to reconsider and withdraw the rejection to claim 5 under 35 U.S.C. § 102(b).

Claims 6 and 7 depend from claim 5 and, as submitted by the Examiner, limit the released fragment to one that is "associated with an increased risk of disease" (claim 6) and further wherein the disease is Alzheimer's (claim 7). Hooper *et al.* teaches that the released APP fragment (known as βA4) is associated with an increased risk of Alzheimer's disease (pg 268, "[t]he deposition of βA4 is currently believed to be the central pathological event in the development of Alzheimer's disease)". Therefore, the teachings of Hooper described above also anticipate claims 6 and 7.

As set forth above with regard to claim 1, Applicant disagrees with the rejection and respectfully submit that claims 6 and 7 are, at least, patentable for being dependent from now allowable independent claim 1. Being dependent claims, the claims incorporate all of the elements of their respective independent claim. In addition, the present invention has been restricted to ACE as the membrane protein for continue prosecution. Further, although Hooper *et al.* may disclose certain methods for screening for agents that are inhibitors of Alzheimer's Disease and in particular those that inhibit a protease associated with the processing of APP, there is no disclosure or suggestion of methods for screening for agents that alter to structure of APP and are therefore allosteric inhibitors as defined in the present invention. Accordingly, Applicant requests the Examiner reconsider and withdraw the rejection to claims 6 and 7 under 35 U.S.C. § 102(b) as being anticipated by Hooper *et al.*

Claim 12 depends from claim 1 and, as asserted by the Examiner, limits the agent to a "small molecule." The inhibitors described by Hooper *et al.*, are alleged by the Examiner to include TAPI-2 and 1, 10-phenanthroline. As such, the Examiner alleges that the teachings of Hooper *et al.* described above also anticipate claim 12.

Applicant respectfully disagrees with the present rejection. As set forth above with regard to independent claim 1, from with claim 12 depends. Being a dependent claim, the claim incorporates all of the elements of its respective independent claim. Claim 1 is not anticipated by Hooper *et al.* because allosteric inhibitors are not disclosed or suggested. Accordingly, Applicant respectfully requests the Examiner to reconsider and withdraw the rejection to claim 12 under 35 U.S.C. § 102(b) as being anticipated by Hooper *et al.*

The Examiner has submitted that Claim 13 depends from claim 1 and, further limits the agent of the claim to a "biomolecule." According to the Examiner, the present specification teaches that biomolecules include molecules that exist or can be produced by living systems "as well as structures derived from such molecules" (citing to paragraph 46 of the published application). The Examiner believes that Hooper *et al.* further teaches that "the effect of various agents (*e.g.*, phorbol esters, transport inhibitors, etc.) on the activity of the secretase can be studied" (pg. 275). The Examiner asserts that phorbol compounds are plant-derived, and phorbol esters are derived from such. Therefore, the Examiner concludes that the teachings of Hooper *et al.* also anticipate claim 13.

Applicant again respectfully disagrees that Hooper *et al.* anticipates any pending claim of the instant application. In particular, as to dependent claim 13, claim 1 upon which claim 13 is dependent, the claim incorporates all of the elements of its respective independent claim. As set forth above, Hooper *et al.* does not disclose or suggest any agent that is an allosteric inhibitor of a membrane protein that alters its processing. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claim 13 under 35 U.S.C. § 102(b) as being anticipated by Hooper *et al.*

Still further, claims 36-38 each depend from claim 1 and, as submitted by the Examiner, limit the host cell to either a mammalian (claim 36), a recombinant (claim 37) or an isolated host cell (claim 38). As described above, the Examiner submits that Hooper *et al.* teaches use of assays using "recombinant cell lines" (which are recombinant and isolated) and

"CHO cells" which are mammalian. Therefore, according to the Examiner, the teachings of Hooper *et al.* as described above also anticipate claims 36-38.

Again, Applicant disagrees with the rejection of claims 36-38 as anticipated by Hooper *et al.* Being dependent claims, claims 36-38 incorporate all of the elements of their respective independent claim and are not anticipated should the reference fail to anticipate the parent claim. As above, Hooper *et al.* fails to disclose or suggest methods for identifying agents that are allosteric inhibitors of a membrane protein. Accordingly, Applicant respectfully requests the Examiner reconsider and withdraw the rejection of claims 36-38 an being anticipated under 35 U.S.C. § 102(b).

Still further, claim 39 which depends from claim 1 and limits the method to one "wherein the agent is contacted with the host cell under substantially physiological conditions" is rejected as anticipated by Hooper *et al.* In particular, the Examiner, asserts that the instant specification teaches in paragraph 65 that such conditions refer to those that "are normally present, or that substantially approximate those normally present, in an extracellular space, on an extracellular surface (*e.g.*, on a cell membrane), in a Golgi network, secretory vesicle, and/or in a complex biological fluid." As such, the Examiner alleges that the phrase "substantially physiological condition" broadly encompasses any screening that takes place with a cell-bound membrane protein because the protein is "on an extracellular surface." As such, the Examiner believes the teachings of Hooper *et al.* described above also anticipate claim 39.

Applicant disagrees with the rejection of claim 39. As set forth above with regard to claim 1, Hooper *et al.* does not disclose or suggest any method that relates to the identification of an agent allosteric effector of a membrane protein. With respect to dependent claim 39, the claim incorporates all of the elements of its respective independent claim, claim 1. Again, as Hooper *et al.* does not anticipate the invention of claim 1, the reference can not anticipate the invention of dependent claim 39. Accordingly, Applicant respectfully requests the Examiner reconsider and withdraw the rejection of claim 39 under 35 U.S.C. § 102(b) as being anticipated by Hooper *et al.*

The Examiner asserts that claims 40 and 41 depend from claim 39 and each encompass conditions comprising the presence of "serum." The Examiner believes that the screening methods taught by Hooper *et al.* with CHO cells inherently comprise serum in the form of fetal bovine serum. The Examiner alleges that in describing the CHO cell assays, Hooper *et al.* references Arribas *et al.*; *Journal of Biological Chemistry* 271(9): 11376-11382; 1996, cited by the Examiner solely to support inherency. According to the Examiner, Arribas *et al.* teaches that the cell medium used in the assays was "supplemented with 10% fetal bovine serum." Therefore, the Examiner believes that the teachings of Hooper *et al.* with respect to CHO cell assays inherently comprise serum, and therefore the teachings of Hooper *et al.* also anticipate claims 40 and 41.

As set forth above with regards to claim 1, Applicant disagrees with the rejection and respectfully submit that claims 40 and 41 are patentable. Claim 1, from which claims 40 and 41 ultimately depend is not anticipated by Hooper *et al.* Accordingly, Applicant respectfully requests the Examiner reconsider and withdraw the rejection of claims 40 and 41 under 35 U.S.C. § 102(b) as being anticipated by Hooper *et al.*

In addition, Applicants submit that the Examiner's argument regarding Arribas *et al.* may not inherently teach the use of serum in the form of fetal bovine serum. The citation to Arribas *et al.* does not explicitly make any discussion of serum, let alone fetal bovine serum. The Examiner is relying on Arribas *et al.* as describing "standard culture conditions" for CHO cells. These conditions as alleged by the Examiner must use serum. To the contrary Arribas *et al.* only describes the use of serum in the cell transfection, mutagenesis, selection and fusion section of the Experimental Procedures. See page 11377, left column. The medium used in the flow cytometry analysis and metabolic labeling sections, the medium is not specifically described as containing serum or any other substantially physiological condition. As Arribas *et al.* does not appear to add anything to the argument of the Examiner, Hooper *et al.* cannot anticipate claims 42-44 because it does not identify with detailed particularity the specific material at issue here or where that material is found such that elements in claims 42-44 are inherently disclosed.

The Examiner asserts that claims 42-44 depend from claim 2 and each encompass the embodiment recited in claim 44, wherein the membrane protein fragment presence is assessed using at least two labeled antibodies for two different epitopes of the membrane protein or a membrane protein fragment. The Examiner believes that the screening methods taught by Hooper *et al.* with CHO cells inherently comprises measurements of ectodomain shedding using two labeled antibodies, including one that binds the extracellular domain (ectodomain) and one that binds the cytoplasmic domain. According to the Examiner, Arribas *et al.* (cited above) teaches, for example, in Figure 3 that "cells were immunostained with antibodies against the L-selectin ectodomain or the HA epitope and analyzed by flow cytometry" (pg 11379). Therefore, the Examiner alleges that the teachings of Hooper *et al.* also anticipate claims 42-44.

As above, Applicant disagrees with the rejection and respectfully submit that claims 42-44 are not anticipated by Hooper *et al.* with, or without the alleged inherent disclosure of Arribas *et al.* Hooper *et al.*, as set forth above, does not disclose or suggest methods for identifying allosteric effectors of a membrane protein. As such, the rejection of claims 42-44 must fail. In addition, as discussed above for claims 40-41, the Examiner raises an inherency argument to include Arribas *et al.* Although, Arribas *et al.* may disclose the use of certain antibodies against the L-selectin ectodomain or the HA epitope, the reference does not disclose or suggest the methods of the present invention. Hooper *et al.* merely cites Arribas *et al.* in relation to an observation that the release of L-selectin can be blocked by metallo-protease and serine-protease inhibitors. The citation to Arribas *et al.*, however, does not explicitly make any discussion of antibodies or other detectably labeled marker, or even contacting a host cell with a detectably labeled marker or antibody. Thus, Hooper *et al.* cannot anticipate claims 42-44 because it does not identify with detailed particularity the specific material at issue or where that material is found such that the elements in claims 42-44 are inherently disclosed.

Accordingly, in view of the comments above, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 42-44 under 35 U.S.C. § 102(b) as being anticipated by Hooper *et al.*

Claim 45 is noted by the Examiner to depend from claim 1 and limits the agent to "allosteric effector of the membrane protein." The Examiner has alleged that the specification does not provide a limiting definition of the term allosteric effector. Therefore, the Examiner has interpreted the term to encompass any agent that changes the structure of the membrane protein. As such, the term is believed by the Examiner to encompass the protease inhibitors described above. The Examiner bases this conclusion on the belief that because inhibition of the cleavage of the membrane protein produced by the inhibitors disclosed in Hooper *et al.* results in a different structure; *i.e.*, an intact membrane protein.

Applicant respectfully disagrees with the Examiner's rejection and have addressed concerns relating to "allosteric effector" above in the discussion of claim 1. With regard to claim 45, the claim has been canceled and the limitation of the claim included in amended claim 1; thus, Applicant submits that the rejection of claim 45 is moot.

As asserted by the Examiner, claim 46 depends from claim 1 and limits the method to one wherein detection of altered processing comprises use of a "flow sorter". The Examiner alleges that Hooper *et al.* further teaches that the "disappearance of the membrane-bound form can be followed by, for example, flow cytometry" (pg 275). Therefore, according to the Examiner, the teachings of Hooper *et al.* also anticipate claim 46.

As above, Hooper *et al.* does not disclose or suggest the method of pending claim 1. Claim 46 is, at least, patentable for being dependent from independent claim 1 which is not anticipated by Hooper *et al.* Any disclosure that relates to the use of flow cytometry does not disclose or suggest another element of the claim missing from the disclosure of Hooper *et al.* Accordingly, Applicant requests the Examiner to reconsider and withdraw the rejection of claim 46 under 35 U.S.C. § 102(b) as being anticipated by Hooper *et al.*

Rejections Under 35 U.S.C. § 103:

Claims 8-10 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hooper *et al.*, *Biochem J.* 321:265-279, 1997, as applied to claim 1 above in the rejections under 35 U.S.C. § 102, and further in view of Mucke *et al.*, U.S. Patent 6,175,057.

The Examiner notes that the teachings of Hooper are described above. In addition, according to the Examiner, Hooper *et al.* further teaches that "considerable effort is being expended to find inhibitors of APP β-secretase and γ-secretase with a view to reducing amyloid burden for Alzheimer's disease." The Examiner, however, believes that Hooper *et al.* does not teach a method of screening wherein an agent that alters processing is from a compound library. The Examiner submits that Mucke *et al.* teaches methods of screening for agents that affect molecular phenomenon associated with Alzheimer's disease. According to the Examiner, Mucke *et al.* teaches that candidate agents include those from "libraries of synthetic or natural compounds" or "combinatorial libraries" including those made by "chemical means," and that candidate agents include those with "functional groups necessary for structural interaction with proteins." The Examiner alleges that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute any of the agents suggested by Mucke *et al.* for the inhibitors used in the method taught by Hooper *et al.*. According to the Examiner, the person of ordinary skill in the art would be motivated to do so in order to identify new inhibitors of the secretases involved in Alzheimer's disease. Further, the Examiner alleges that a person of ordinary skill in the art would have a reasonable expectation of success because the method simply requires using the libraries described by Mucke *et al.* in the screening assays fully described by Hooper *et al.*.

The Applicants respectfully disagree with the Examiner's rejection and do not acquiesce to the reasoning used to support the rejection. As above, Hooper *et al.* does not disclose or suggest methods for the identification of an agent that is an allosteric effector of a membrane protein as set forth in claim 1 as currently amended. Applicant submits that the references cannot render the claims 8-10 obvious because, for example, the claims are dependent

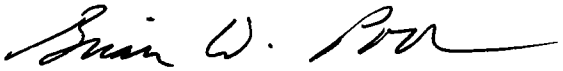
from independent claim 1. Mucke *et al.* discusses, for example, libraries of synthetic or natural compounds but fails to provide any element missing from Hooper *et al.* Thus, even if the references were combined (which, as described below, they cannot be), the references could not render obvious the present claim 1 because each reference either combined or taken alone does not teach or suggest a method as set forth in amended claim 1.

In addition, contrary to the Examiner's assertions, Hooper *et al.* and Mucke *et al.* cannot be combined to support an obviousness rejection. According to MPEP 2143 (citing *KSR v. Teleflex*, 82 USPQ2d at 1396 (2007)), "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." Here, the Examiner has merely stated that the references could be combined because it would have been obvious o substitute any of the agents suggested by Mucke for the inhibitors used in the method taught by Hooper because of motivation to identify new inhibitors of the secretases involved in Alzheimer's Disease. Such a general motivation and reason seems insufficient to provide a reason why an ordinarily skilled artisan would be prompted to combine the references. This is particularly the case where Hooper *et al.* does not disclose or suggest a method for identifying any agent the is an allosteric effector of a membrane protein. The inhibitors of Hooper *et al.* appear to interact with the secretase and not with the membrane protein or bind with the recognition site for the secretase on the enzyme thereby blocking binding. Thus, Applicant respectfully submits that Hooper *et al.* when considered alone, or in combination with Mucke *et al.* does not disclose or suggest the method recited in the pending claims. Accordingly, for the reasons set forth above, claims 8-10 would not have been obvious to one of ordinary skill in the art at the time of invention; therefore, the Applicants request that the rejection of claims 8-10 under 35 U.S.C. § 103 as being unpatentable over Hooper *et al.* further in view of Mucke *et al.* be reconsidered by the Examiner and withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,



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